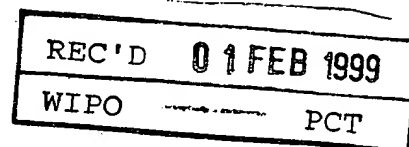


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PATENT- OCH REGISTRERINGSVERKET
Patentavdelningen

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Intyg
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This is to certify that the annexed is a true copy of the documents as originally filed with the Patent- and Registration Office in connection with the following patent application.

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För Patent- och registreringsverket
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TITLE: METHOD AND DEVICE FOR CALCULATING DIALYSIS EFFICIENCY

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FIELD OF THE INVENTION

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The present invention relates to a method and device for calculating dialysis efficiency. More specifically, the invention relates to a method and device for obtaining a concentration of urea and/or other solutes present in blood.

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The present invention is intended to be used for a dialysis treatment, such as hemodialysis, hemodiafiltration or hemofiltration. It can also be used for peritoneal dialysis. However, the invention is not limited to the above-mentioned treatment modes, but can also be used for other medical or non-

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BACKGROUND ART

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A method and device for calculating dialysis efficiency is disclosed in Swedish Patent Application No. 9702074-7 filed 1997-06-02, Applicant Gambro AB. In said Patent Application, a whole body relative efficiency is calculated. The calculation uses a removed urea concentration curve obtained by a urea monitor during dialysis. The result is a value of the removed mass of urea m_{rem} from which can be calculated total accumulated urea mass in the body, whole body dialysis dose Kt/V , solute removal index SRI, etc.

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It is, according to said Patent Application, necessary to obtain a value of the initial concentration of urea, for example in blood in order to be able to fully characterize the dialysis treatment. Another approach also described is to obtain a value of the total body water volume V of the patient, whereupon the urea concentration in the patient can be calculated.

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A number of different approaches to obtain said concentration of urea are given in said Patent Application, like blood sample or equilibrated dialysis solution before the start of the treatment. These methods are not unproblematic and there is a desire to eliminate manual intervention. Moreover, blood samples need to be taken before the initiation of dialysis treatment. As soon as the treatment starts, the initial blood concentration of urea is diluted due to cardio-pulmonary recirculation and access recirculation. Thus, care must be exercised to obtain the initial urea concentration before it is compromised.

The object of the present invention is to provide a method and a device for obtaining the initial urea concentration in blood before the dialysis treatment, to be used in the invention according to Swedish Patent Application No. 9702074-7 for calculating many essential dialysis related parameters of a patient.

Specifically, it is possible to use the total body urea mass m_0 , and the initial urea concentration c_0 in blood obtained according to the present invention for calculating the distribution volume V of urea in the body. This parameter V is expected to be constant from the end of one treatment to the end of the next and could be used as an alternative to dry body weight as a parameter for determining the required ultrafiltration during a dialysis treatment. Moreover, the distribution volume V could be a long term marker for the general status of the patient.

A method of determining the dialysance of a dialyser used during dialysis treatment is disclosed in EP 658 352 filed by Hospal AG. According to this method, a disturbance is generated in the fresh dialysis solution before the dialyser and the resultant effect in the dialysate after the dialyser is measured. Normally, the disturbance is induced in the conductivity of the dialysis solution. The method gives the effective ionic dialysance for the dialyser and the effective plasma conductivity.

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SUMMARY OF THE INVENTION

In clinical studies this ionic dialysance for a dialyser measured according to EP 658 352 has been shown to agree well with the effective plasma water clearance of that dialyser for urea (K_e), i.e. plasma water clearance corrected for recirculation, pulmonary recirculation as well as access recirculation.

The definition of clearance implies that the urea mass removal rate equals the product of the effective plasma water clearance (K_e) and plasma water concentration (C_{pw}) of urea in the blood returning from the body. The difference between dialyzer clearance and effective dialyzer clearance is that for dialyzer clearance the denominator should be plasma water concentration in the blood entering the dialyzer while for effective dialyzer clearance the denominator should be plasma water concentration in the blood returning from the body. Due to recirculation this concentration in the blood entering the dialyzer differs from the concentration in the blood returning from the body.

The urea mass removal rate is measured by the urea monitor as the product of dialysate flow rate (Q_d) and the urea concentration in the spent dialysate (C_d). We can therefore equate the two expressions for urea mass removal rate from plasma water and into the spent dialysate

$$K_e \times C_{pw} = Q_d \times C_d$$

In this equation, K_e is obtained by the method of EP 658 352 or a similar method, while Q_d and C_d are obtained by the urea monitor. Thus, C_{pw} can be calculated.

There is, however, an additional effect that has to be taken into account. Due to internal resistance in the body to urea transport, a urea gradient starts to develop within the body from the start of a dialysis treatment. This means that the urea concentration is gradually differing more and more in different parts of the body, and the urea concentration in the blood returning from the body, which is used in the

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calculations above, is no longer representative of the mean urea concentration in the body. It is therefore only at the beginning of a treatment while urea is equally distributed in the body that the calculation above can be used to find the mean urea concentration in the body.

The urea monitor is programmed to find the starting value for dialysate urea c_{d0} by interpolating backwards along the concentration curve using measurements from 20 to 5 minutes after treatment start, which is defined as the time when the measured dialysate urea concentration c_d is steadily above a predetermined low concentration value. Due to time constants in the monitor this starting value will not catch the initial decrease in urea due to the development of recirculation, so this initial dialysate urea concentration c_{d0} will be representative of conditions with recirculation already developed. Using this starting value of c_d in the formula above, together with a measurement of effective clearance (K_e) performed by for example the method described in EP 658 352, will produce the initial plasma water concentration c_{pw0} of urea in the blood returning from the body. At the start, before any gradients have developed in the body, this will also be the mean plasma water concentration in the body. The measurement of effective clearance K_e should preferably be performed as soon after the initial 20 minutes (for the interpolation of initial dialysate urea) as possible to avoid unintentional changes in clearance, and all factors affecting clearance such as blood and dialysate flows should be kept constant during this period.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a schematic view of a dialysis machine intended for hemodialysis including a urea monitor and where the invention can be used.

Fig. 2 is a schematic view similar to Fig. 1, but with the urea monitor integrated in the dialysis machine.

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Fig. 3 is a schematic view similar to Fig. 1 of a dialysis machine adapted for predilution hemofiltration.

Fig. 4 is a schematic view similar to Fig. 2 of a dialysis machine adapted for postdilution hemofiltration.

Fig. 5 is a diagram over concentration values obtained from the urea monitor in the dialysis machine according to anyone of Figs. 1 - 4.

DESCRIPTION OF PREFERRED EMBODIMENTS

Fig. 1 is a schematic diagram of a dialysis machine in which the invention according to Swedish Patent Application No. 9702074-7 and the present invention can be practised. The dialysis machine provides means for replacing the renal function of a mammal if the renal function is impaired or completely absent.

The blood from a patient is taken out into an extracorporeal circuit 2 including a filter or dialyzer 1, including a semipermeable membrane 3. The blood passes along one side of the membrane. At the other side of the membrane, a dialysis fluid is circulated by the dialysis machine 4.

The dialysis fluid is usually prepared by the machine from one or several concentrates and water to form a dialysis fluid having the desired properties. Thus, the machine disclosed in Fig. 1 comprises a water inlet 5, two concentrate inlets 6 and 7, and two concentrate metering pumps 8 and 9. A first main pump 10 propels the fresh dialysis fluid to the dialysis side of the dialyzer into contact with the membrane.

A second main pump 11 passes the effluent fluid, dialysate, from the dialyzer, namely the inlet dialysis fluid and any ultrafiltrate removed from the blood via the filter, further on to an outlet 12 and to the drain.

A by-pass line 13 is arranged between the first 10 and the second pump 11. Several valves 14,15,16 are arranged for controlling the flow of dialysis fluid. The valves and the pumps are controlled by a computer 17 as schematically shown by

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several lines in Fig. 1. Of course, the dialysis machine is provided with several other means as is conventional. These other means are not disclosed, since they are not relevant for the operation of the present invention.

5 The first main pump 10 is driven with a speed so that the dialysis fluid delivered to the dialyzer is substantially constant, e.g. 500 ml/min. The second main pump 11 is driven with a slightly higher speed so that the effluent fluid, called the dialysate, has a flow rate of e.g. 515 ml/min. This
10 operation generates a low pressure at the dialysate side of the dialyzer, which is suitable for removing 15 ml/min of ultrafiltrate fluid from the blood, i.e. plasma water. During a treatment of 4 hours, such ultrafiltration results in a fluid removal from the patient of 3,6 litres. Of course, the dialysis
15 machine is operated so that the treatment prescribed to the patient is fulfilled.

In the effluent line from the dialysis machine is placed a urea monitor 18, which measures the urea concentration c_d in the effluent dialysate. The monitor can be positioned inside the
20 dialysis machine or completely outside the dialysis machine. The urea monitor can be of the type disclosed in WO 96/04401.

The urea monitor is shown connected to the computer 17 of the dialysis machine. However, the monitor can have a computer of its own.

25 The urea sensor or the dialysis machine also includes means for measuring the flow rate of the effluent dialysate, Q_d . The computer 17 is arranged to provide concentration values c_d as well as values of the total mass of urea U removed during the treatment as the integral of $Q_d \cdot c_d$. The concentration values
30 are taken continuously so that a concentration curve c_d can be obtained from the urea sensor as well as a mass curve U .

Fig. 2 discloses a similar dialysis machine as Fig. 1. The main difference is that the urea monitor 19 is placed between the dialyzer 1 and the second main pump 11 and before
35 the outlet of the bypass line.

Fig. 3 discloses a similar dialysis machine as Fig. 1, but adapted for hemofiltration or hemodiafiltration. The only

difference is that there is included an infusion line 20 including an infusion pump 21. The infusion line 20 starts from the outlet of the first main pump 10 and ends at the blood inlet side of the dialyzer, for providing an infusion fluid to the blood before the dialyzer, called predilution. The urea monitor 22 is arranged in the effluent dialysate line after the second pump 11.

Fig. 4 discloses a similar dialysis machine as Fig. 2, but adapted for hemofiltration or hemodiafiltration and providing an infusion fluid to the blood after the dialyzer, called postdilution. The urea monitor 23 is placed before the second main pump 11 and before the outlet of the bypass line.

Finally, Fig. 5 discloses a typical urea concentration curve c_d obtained from the urea sensor. As appears from the figure, the curve is very irregular and includes several dips. These dips are obtained when the dialysis machine is connected for selfcalibration, in which case valve 16 is opened and valves 14 and 15 are closed.

For the operation of the invention according to Swedish Patent Application No. 9702074-7, please refer to that application, which is included herein by reference. The result is that a removed urea concentration curve c_d is obtained as disclosed in Fig. 5. The initial values, for example values obtained from 5 minutes to 20 minutes, are used for extrapolating an initial urea concentration c_{d0} at the start of the dialysis treatment.

The start of the dialysis treatment is defined as the time when the urea concentration is steadily above a predetermined low concentration value. The actual determination of concentration values are initiated five minutes after determining such a steady condition in order to be sure that the treatment is going on and will not be discontinued.

In order to obtain a measurement of the effective dialysanse of the dialyser, a disturbance is induced in the fresh dialysate by operating the pumps 8 and 9 controlled by the computer 17. The disturbance can be an increase in the ionic content of the dialysis fluid by operating both pumps 8 and 9

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and increase the speed of these pumps by for example 10% during 60 seconds.

The resultant disturbance is measured after the dialyser, for example by a conductivity meter, and the measurement result is processed for example as described in EP 658 352 to obtain the effective dialysance K_e . The measurement is performed as soon as possible and preferably after the initial 20 minutes and without changing any of the parameters influencing on the dialysance of the dialyser, like blood flow rate and dialysate flow rate. EP 658 352 is incorporated in the present application by reference.

If the disturbance is a step change in the conductivity, produced by pumps 8,9 the dialysance of the dialyser can be determined according to equation (see EP 547 025, the contence of which is included in the present application by reference):

$$D_e = Q_d [1 - (C_{dout2} - C_{dout1}) / (C_{din2} - C_{din1})]$$

where

D_e = effective dialysance of the dialyser

Q_d = effluent dialysate flow

C_{dout1} and C_{dout2} = concentration in the effluent dialysate

C_{din1} and C_{din2} = concentration in the introduced dialysis fluid

Indexes 1 and 2 indicates before and after the step change. The introduced concentration can be measured or be determined by the set values of the concentration pumps.

The value of the effective dialysance is used for determining the initial urea concentration in blood at the start of the treatment according to the formula:

$$C_{pw0} = Q_d \times C_{d0} / K_e$$

The plasma urea concentration can then be corrected for protein content in the blood. This correction is fairly constant for the normal range of protein concentrations, which allows the use of the same correction factor for all patients, although

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the best accuracy is achieved if the true protein content is used.

It is noted that the urea monitor includes a conductivity meter, so there need not be any separate conductivity meter after the dialyser for the measurement according to the present invention.

Instead of measuring the conductivity before the dialyser, the set values of the disturbance can be used.

The disturbance can be induced in different ways.

Another approach is to use a small dose of urea which is introduced in the fresh dialysis fluid just before the entrance into the dialyser as disclosed in Fig. 2. A pump 24 is connected to the inlet of the dialyser after valve 14. The pump is also connected to a small bag 25 containing a predetermined quantity of urea dissolved in water or dialysis fluid and having a predetermined concentration. The disturbance induced by this introduction of urea in the dialysis circuit is measured by the urea monitor upstream of the dialyser and the result is evaluated by the computer 17. It should be mentioned that by integrating the surface of the disturbance, the mass of urea reaching the urea monitor can be calculated. The difference from the amount introduced, which is known, must have passed through the membrane of the dialyser into the blood of the patient. Thus, the effective dialysance D_e or the effective clearance K_e for urea of the dialyser can be calculated, according to the formula:

$$D_e = Q_d \times (1 - S_{out}/S_{in})$$

where:

D_e = effective dialysance of the dialyzer

Q_d = dialysate flow emitted from the dialyzer

S_{out} = integral of $(cd(t) - cd_0)$ during the disturbance in the flow emitted from the dialyzer

S_{in} = integral of $(cd(t) - cd_0)$ during the disturbance in the flow entered into the dialyzer

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Of course, the bag 25 can include sodium ions instead of urea and the conductivity meter of the urea monitor can be used for measuring the increased conductivity due to the introduction of extra sodium ions. It is known that the clearance for sodium ions is approximately equal to the clearance of urea. Other types of ions or substances can also be used as well as decreases instead of increases of the concentration or conductivity of the fresh dialysis solution.

If pure water is added, i.e. water without any ions or other substances, the integral given above will be negative, and the surface will have a relationship with the amount of added water.

It is noted that the integral S_{in} times the dialysate flow Q_d equals the amount of material added to the solution. Thus, if urea is added, S_{in} need not be measured but can be calculated from the known amount of urea and the dialysate flow in the addition to the dialysate. Possibly, a correction for dilution is required.

The same applies if sodium is used, whereby $S_{in} \times Q_{din}$ equals the addition of material in excess of the normal amount, which normally is known in advance.

It is also apparent that the material can be added in any way that enables the measurement at the outlet side of the dialyzer, i.e. the disturbance need not be rectangular, but can have any shape. Thus, the introduction flow rate of the material in the dialysate flow is of no importance as soon as it is of such a flow rate that the resultant disturbance is not too small to be measured and not too large to be outside the measuring capability of the measurement instrument at the outlet side of the dialyzer. Of course, the disturbance must also be compatible with the body.

The added material can be dissolved in water, whereby the dilution effect should be considered when introducing the material in the circuit. Another approach would be to dissolve the material in normal dialysis fluid, for example dissolve a known amount of urea in a known amount of dialysis fluid. This dissolution can be performed in advance, so that the material is

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delivered in bag 25 to be connected to the dialysis circuit. Alternatively, the material can be delivered in powder form, for example a known amount of urea in powder form in a bag 25. The bag is connected to the dialysis machine, and the pump 24 is operated to introduce a known amount of dialysis fluid in the bag to dissolve the amount of material. After dissolution, the pump 24 is reversed and the material in the bag is introduced into the circuit.

The main pump 16 can be operated so that the total amount of fluid entering the dialyser is constant, i.e. the flow rate of pump 16 and pump 24 is constant. For example, if pump 24 is operated at a speed of 50 ml/min, pump 16 is reduced to 450 ml/min during the introduction period and returned to 500 ml/min after the introduction of the substance.

It is also possible to introduce a disturbance at the other side of the membrane as suggested in Fig. 2 by pump 26 and bag 27. In the same way as with pump 24 and bag 25, an introduction of urea of a known concentration and amount will result in an increase of the urea concentration in the dialysate reaching the urea monitor. This disturbance can be integrated and processed for obtaining the clearance of the dialyser.

The added material can be fresh dialysis fluid obtained from the dialysis machine, but of a higher (or lower) ionic strength or osmolarity, whereby the conductivity is measured. Alternatively, fresh dialysis fluid can be added, which comprises no urea, and the resulting diluting effect on urea in blood can be determined on the dialysate side by the urea monitor.

The added material, such as urea can be diluted in water or dialysis fluid as indicated above. Moreover, the material can be delivered in powder form in a bag 27 and dissolved in blood by reversing pump 26 and introducing blood in the bag for dissolution of the material and then operating the pump 26 in the normal direction for introducing the material in the circuit.

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The time of the measurement can be shortened by using the exponential behaviour of the disturbance for calculating the result.

5 When using the integral method, the time can be shortened in the same way by estimating the error if the measurement is terminated in advance.

10 Hereinabove, the invention has been described in details by means of several embodiments of the invention. The different features in the different embodiments can be combined in further different ways, which combinations are intended to be within the scope of the present invention. The invention is only limited by the appended patent claims.

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Huvudfören Kassan

PATENT CLAIMS

1. Method of calculating the concentration of a substance in blood of a mammal

5 passing the blood through a dialyser comprising a semipermeable membrane and passing a dialysing fluid at the other side of the membrane;

measuring the concentration c_d of said substance in said fluid emitted from said dialyser;

characterized by

10 introducing a disturbance in said dialyser and calculating the effective dialysance K_e of said dialyser; and

calculating the concentration c_{pw} of said substance in blood.

2. Method according to claim 1, **characterised by**

15 measuring the dialysate fluid flow rate Q_d and calculating the concentration of said substance in blood by the formula

$$c_{pw} = c_d \times Q_d / K_e$$

3. Method according to claim 2, **characterised by**

20 measuring the concentration c_d of said substance in said fluid to obtain a curve over the concentration versus time;

calculating the initial mass m_0 of said substance in the blood;

25 calculating the initial concentration c_{pw0} of said substance in the body;

calculating the distribution volume V of said substance in the body of said mammal according to the formula

$$V = m_0 / c_{pw0}$$

4. Method according to claim 1, 2 or 3 **characterised by**

30 calculating the effective dialysance K_e of said dialyser by introducing a disturbance in said dialyser in the nature of a change of the concentration of a second substance in said dialysis fluid introduced in the dialyser;

35 measuring the resulting change in the concentration of said second substance in said dialysis fluid leaving the dialyser for calculating the effective dialysance K_e of said dialyser.

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5. Method according to anyone of the previous claims, **characterised** in that the first substance is urea and the second substance is sodium ions, conductivity or urea.

6. Apparatus for calculating the concentration of a substance in blood of a mammal, comprising:

means for passing the blood through a dialyser comprising a semipermeable membrane and means for passing a dialysing fluid at the other side of the membrane,

means for measuring the concentration c_d of said substance in said fluid emitted from said dialyser,

characterized by

means for introducing a disturbance in said dialyser and for calculating the effective dialysance K_e of said dialyser; and means for calculating the concentration c_{pw} of said substance in blood.

7. Apparatus according to claim 6, **characterised by** means for measuring the dialysate fluid flow rate Q_d and for calculating the concentration of said substance in blood by the formula

$$c_{pw} = c_d \times Q_d / K_e$$

8. Apparatus according to claim 7, **characterised by** means for measuring the concentration c_d of said substance in said fluid to obtain a concentration curve;

means for calculating the initial mass m_0 of said substance in the body, and

means for calculating the distribution volume V of said substance in the body of said mammal according to the formula

$$V = m_0 / c_{pw0}$$

9. Apparatus according to claim 6, 7 or 8 **characterised by** means for calculating the effective dialysance K_e of said dialyser by introducing a disturbance in said dialyser in the nature of a change of the concentration of at least a second substance in said dialysis fluid introduced in the dialyser;

means for measuring the resulting change in the concentration of said second substance in said dialysis fluid leaving the dialyser, and

means for calculating the dialysance of said dialyser.

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10. Apparatus according to anyone of claims 6 - 9,
characterised in that the first substance is urea and the second
substance is sodium ions, conductivity or urea.

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Huvudföreläsaren Kallén

ABSTRACT

Method and apparatus for calculating the concentration of a substance in blood of a mammal. Blood from the mammal is passed through a dialyser having a semipermeable membrane and a dialysing fluid is passed at the other side of the membrane. The concentration of urea c_d is measured in the dialysate emitted from the dialyser and the dialysate fluid flow rate Q_d . A disturbance is introduced in the dialyser whereupon the effective dialysance K_e of the dialyser is calculated. Finally, the concentration of urea in blood is calculated by the formula

$$C_{pw} = c_d \times Q_d / K_e$$

By using the curve of urea concentration c_d versus time in the dialysate, it is possible to calculate the initial mass m_0 of urea in the blood. Finally, the distribution volume V of urea in the is calculated according to the formula

$$V = m_0 / C_{pw}$$

(Fig. 1)

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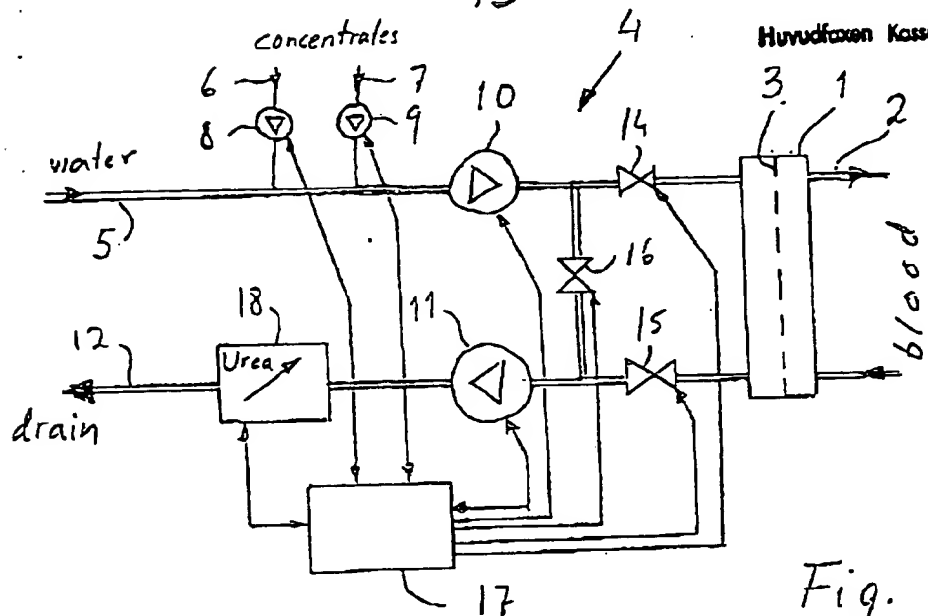
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Fig. 1

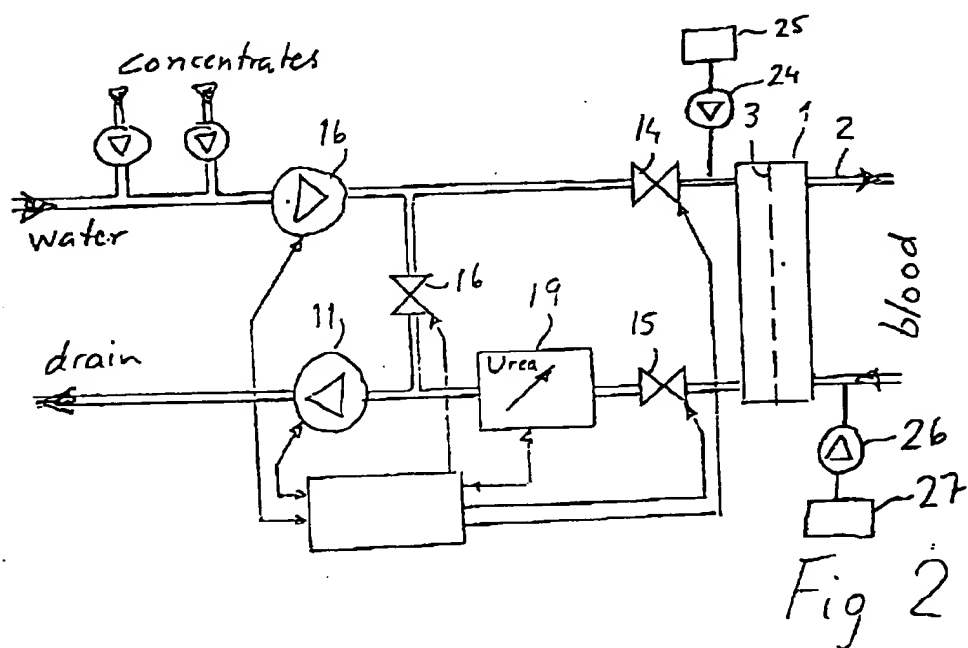


Fig 2

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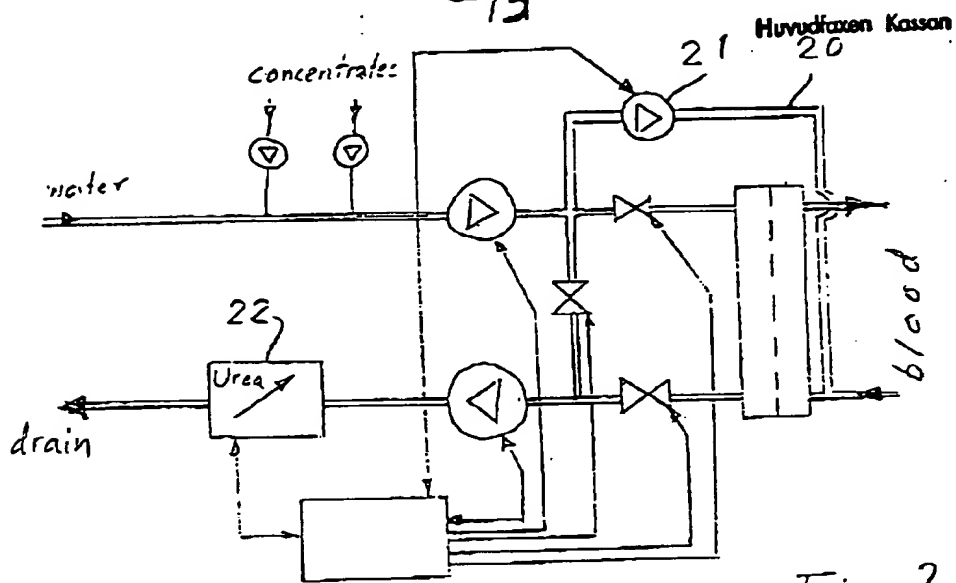


Fig. 3

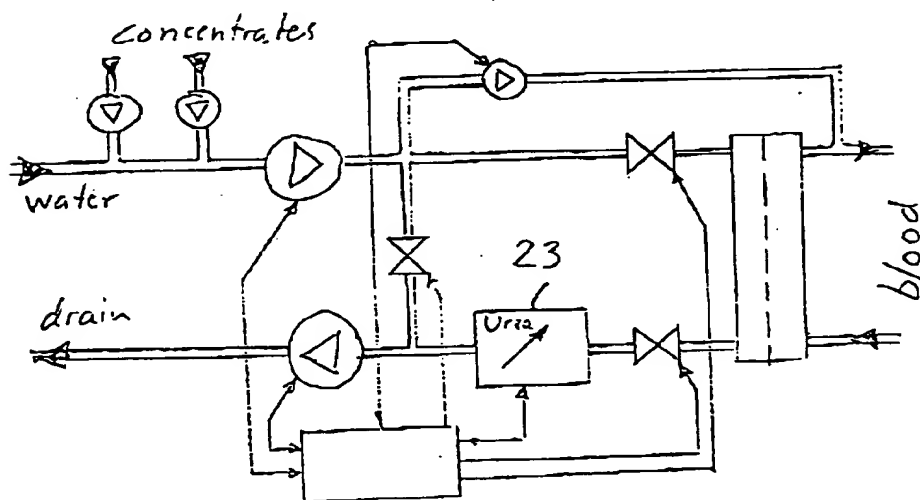


Fig 4

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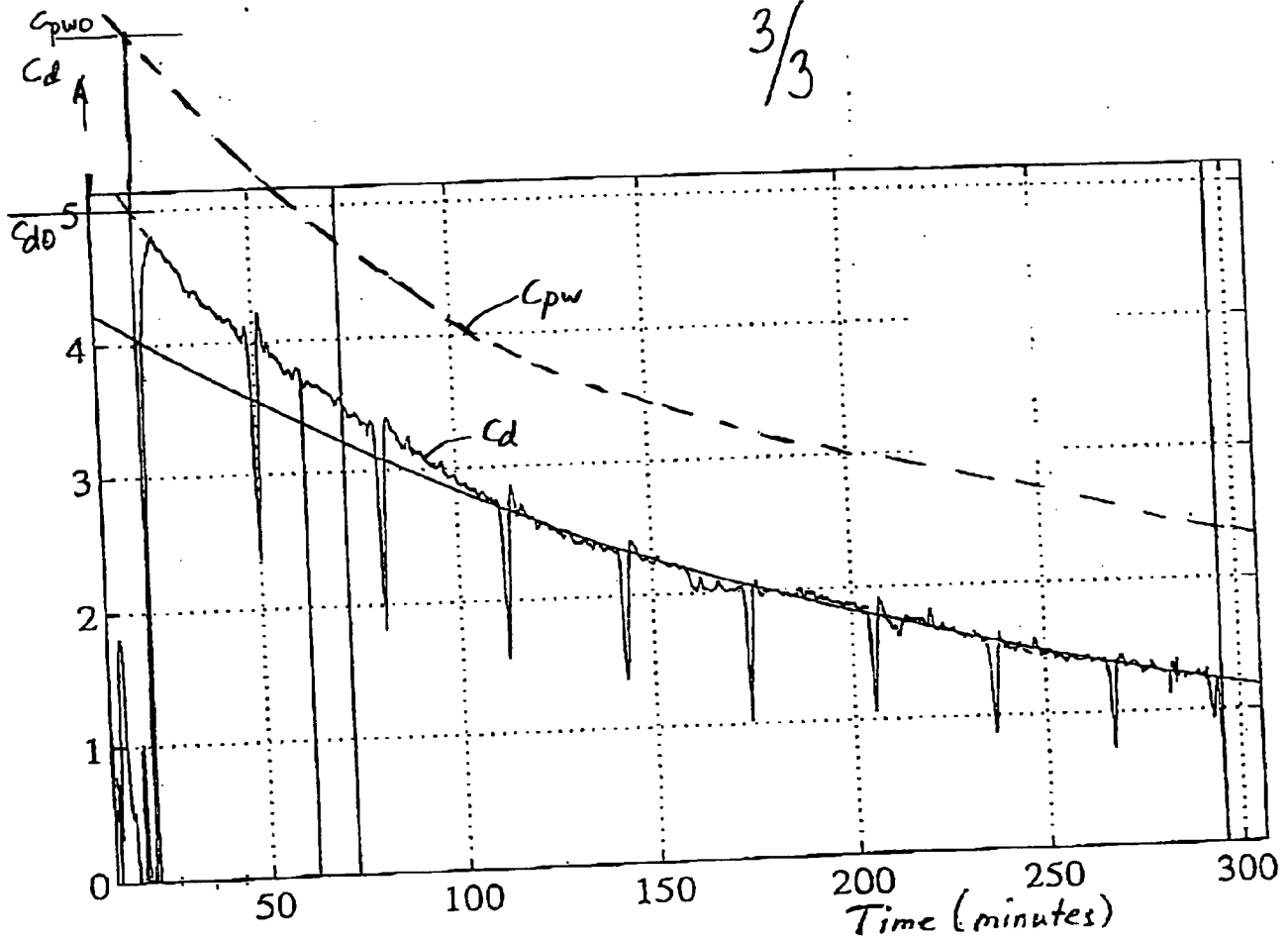


Fig. 5